

ORIGINAL ARTICLE

Patterns of complications following intraoperative radiofrequency ablation for liver metastases

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Abstract

Background: Intraoperative radiofrequency ablation (IRFA) is added to surgery to obtain hepatic clearance of liver metastases. Complications occurring in IRFA should differ from those associated with wedge or anatomic liver resection.

Methods: Patients with liver metastases treated with IRFA from 2000 to 2010 were retrospectively analysed. Postoperative outcomes are reported according to the Clavien–Dindo system of classification.

Results: A total of 151 patients underwent 173 procedures for 430 metastases. Of these, 97 procedures involved IRFA plus liver resection and 76 involved IRFA only. The median number of lesions treated by IRFA was two (range: 1–11). A total of 123 (71.1%) procedures were carried out in patients who had received preoperative chemotherapy. The mortality rate was 1.2%. Thirty (39.5%) IRFA-only patients and 45 (46.4%) IRFA-plus-resection patients presented complications. Immediate complications ($n = 4$) were associated with IRFA plus resection. American Society of Anesthesiologists (ASA) class, previous abdominal surgery or hepatic resection, body mass index, number of IRFA procedures, portal pedicle clamping, total vascular exclusion and preoperative chemotherapy were not associated with a greater number of complications of Grade III or higher severity. Length of surgery >4 h [odds ratio (OR) 2.67, 95% confidence interval (CI) 1.1–6.3; $P < 0.05$] and an associated contaminating procedure (OR 3.72, 95% CI 1.53–9.06; $P < 0.005$) led to a greater frequency of complications of Grade III or higher.

Conclusions: Mortality and morbidity after IRFA, with or without resection, are low. Nevertheless, long interventions and concurrent bowel operations increase the risk for septic complications.

Received 4 February 2014; accepted 7 April 2014

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Introduction

Intraoperative radiofrequency ablation (IRFA) to treat patients with unresectable liver metastases has now been in use for more than 10 years.^{1,2} As it is a relatively new surgical technique, assessments of both its technical added value and associations with potential morbidity and mortality are crucial. Prospective studies examining patients with unresectable colorectal liver metastases (CLM) have concluded that longterm survival can be achieved using radiofrequency ablation (RFA) in an intraoperative setting.^{3,4} In patients with complex CLM initially judged to be unresectable, rates of overall survival of 57.6% at 30 months⁴ and

43.0% at 5 years³ have been reported. Per-lesion rates of local recurrence of ablated metastases were 6.5%⁴ and 4.0%,³ which are comparable with those reported after hepatectomy in patients with borderline surgical resectability.^{5,6} These studies provide further evidence for the safety and effectiveness of the clinical use of IRFA as a complementary technique to resection, and it is already employed with encouraging outcomes in specialized centres across the world.^{7–10} The negative prognostic impact of postoperative complications on survival after hepatic resection of CLM has been well documented.^{11–13} Thus, it is important that postoperative complications associated with surgery for liver metastases are minimized if potential survival is to be optimized.

The aim of the present study was to evaluate retrospectively the morbidity and mortality rates of IRFA, either performed alone or in combination with resection, at a single centre over a 10-year period.

Materials and methods

All patients surgically treated for liver metastases with IRFA without laparoscopy between 2000 and 2010 were retrospectively identified from data collected prospectively (Medlog 2000®; Medlog, Inc., San Antonio, TX, USA) in the Digestive Tumour Unit, Institut Bergonié, Bordeaux, France. Subsequent procedures were considered as separate and independent in all per-procedure analyses. This study was approved by the study centre's institutional review board and carried out in compliance with the Helsinki Declaration. No exclusions were made on the basis of the aetiology of the liver metastasis. For each patient, surgical decisions were made by a multidisciplinary team that included oncologists, radiotherapists, radiologists and surgeons. All operations were performed by the same surgeon. Intraoperative assessment always included a complete exploration of the peritoneal cavity, liver mobilization and liver intraoperative ultrasound (IOUS) examination. The choice of IRFA or IRFA combined with resection was made during the surgery after IOUS imaging of the liver based on three aspects: unresectability of lesions; size of lesions, and sparing of the functional parenchyma (IRFA was the preferred method when possible). Deep, single-nodule lesions, of <35 mm in diameter and far from a main biliary duct but possibly close to a hepatic vein were candidates for ablation, whereas superficial, multi-nodule lesions of >35 mm or located close to a main biliary duct were treated with resection.

Intraoperative radiofrequency ablation procedures were performed using straight needles (Integra ME GmbH, Tuttlingen, Germany) perfused with isotonic saline serum and connected to a generator (Elektrotom 106 HFTT; Berchtold GmbH & Co. KG, Tuttlingen, Germany). The needle diameter was 1.2 mm and the active tips were 10 mm, 15 mm or 20 mm long. The needle was introduced and treatment performed using ultrasound guidance. The total energy (joules) delivered per impact was calculated by the generator's computer. The duration and number of impacts depended on the size of each lesion. Vascular occlusions were sometimes required: a Pringle manoeuvre was performed if the lesion was located close to a portal vessel, but not in the proximity of a main portal branch, where IRFA is contraindicated. A hepatic vein close to the lesion could be clamped. Up to all three hepatic veins could be clamped and portal blood flow interrupted; this prevented the cooling of the target and thus achieved greater heat delivery during the treatment.¹⁴

The terminology for hepatectomy is as described by Couinaud.¹⁵ Parenchymal division was performed using the Kelly clamp-crushing method and completed by a bipolar vessel-sealing clamp (Ligasure®; Covidien, Inc., Mansfield, MA, USA) for vascu-

lar and biliary structure control. Hepatectomies were usually conducted under intermittent pedicular clamping.¹⁶

Complications were exhaustively recorded using the classification described by Dindo *et al.*¹⁷ and categorized according to the time of symptom onset after surgery as immediate (<24 h), early (1–30 days) or delayed (>30 days). Hepatic failure was defined according to the definition of the International Study Group of Liver Surgery¹⁸ using biological and clinical signs of hepatocellular dysfunction (ascites, encephalopathy, jaundice). Severe hepatic failure was defined by the conjunction of prothrombin time of <50% and serum bilirubin of >50 µmol/l on postoperative day 5. Hepatobiliary complications included liver abscesses or collection, biliary stenosis, biliary fistula and biloma. Main parietal complications encompassed wound abscesses, whereas intra-abdominal extrahepatic complications were abscesses, anastomotic leakage and occlusion.

Statistical considerations

Correlations between the occurrence of complications of Grade III or higher and pre- and intraoperative variables were established using univariate analysis (chi-squared and Fisher's tests for qualitative data and the Wilcoxon non-parametric test for quantitative data).

All variables that were found in univariate analysis to have a statistically significant association at the $P < 0.05$ level were included in the multivariate model using logistic regression with a stepwise descendant procedure. The odds ratio (OR) with a 95% confidence interval (95% CI) was chosen as the measure of association. All results are described per procedure. Statistical analyses were performed using PASW Statistics Version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 339 patients were treated for liver metastases and registered in a prospective database between 2000 and 2010. The present retrospective study includes 151 (44.5%) patients treated with IRFA. Of these patients, 22 (14.6%) were treated twice and thus a total of 173 procedures for 430 liver metastases were performed. All data are presented per procedure. Patient characteristics are presented in Table 1 and intraoperative variables are shown in Table 2. A total of 22 (12.7%) procedures involved the total vascular exclusion of the liver. Table 3 shows the perioperative outcomes and complications. Overall morbidity and mortality rates were 43.4% (95% CI 36.0–50.7; $n = 75/173$) and 1.2% ($n = 2$), respectively. Complications of Grade III or higher occurred in 36 procedures (20.8%, 95% CI 14.8–26.9). Overall, 57 (76.0%) complications occurred between 24 h and 30 days after surgery. Two deaths were registered in, respectively, an elderly woman with severe obesity who died of septicaemia and a young male with anastomotic leakage after concomitant gastric surgery. Hepatic collections included two hepatic abscesses on the IRFA site, treated by percutaneous drainage and antibiotics. Two

Table 1 Characteristics of patients and tumours treated with intraoperative radiofrequency ablation (IRFA) alone or with IRFA plus hepatic resection across procedures for liver metastases. Data are shown per procedure

	IRFA alone	IRFA plus resection	Total
Procedures, <i>n</i> (%)	76 (43.9%)	97 (56.1%)	173 (100%)
Age at surgery, years, median (range)	63.0 (27–98)	63.0 (21–82)	63.0 (21–98)
ASA score, <i>n</i> (%)			
1	17 (22.4%)	34 (35.4%)	51 (29.7%)
2	50 (65.8%)	52 (54.2%)	102 (59.3%)
3	9 (11.8%)	10 (10.4%)	19 (11.0%)
Sex, male, <i>n</i> (%)	44 (57.9%)	61 (62.9%)	105 (60.7%)
Body mass index, median (range)	25.2 (16.5–39.1)	25.4 (18.3–34.3)	25.3 (16.5–39.0)
Prior abdominal surgery, <i>n</i> (%)	58 (76.3%)	80 (82.5%)	138 (79.8%)
Prior hepatectomy, <i>n</i> (%)	19 (25.0%)	26 (26.8%)	45 (26.0%)
Preoperative chemotherapy ^a , <i>n</i> (%)	48 (63.2%)	75 (77.3%)	123 (71.1%)
Liver primary	2 (2.6%)	1 (1.0%)	3 (1.7%)
Liver secondaries	74 (97.3%)	96 (99.0%)	170 (98.3%)
Isolated liver metastases	54 (71.1%)	77 (79.4%)	131 (75.7%)
Synchronous metastases	39 (51.3%)	58 (59.8%)	97 (56.1%)

^aMedian of nine cycles.

ASA, American Society of Anesthesiologists.

Table 2 Description of intraoperative variables in patients treated with intraoperative radiofrequency ablation (IRFA) alone or with IRFA plus hepatic resection. Data are shown per procedure

	IRFA only	IRFA plus resection	Total
Procedures, <i>n</i> (%)	76 (43.9%)	97 (56.1%)	173 (100%)
Length of surgery, h, median (range)	3.5 (1.2–8.5)	3.5 (1.3–7.5)	3.5 (1.2–8.5)
Lesions treated by IRFA, <i>n</i> , median (range)	2 (1–11)	2 (1–8)	2 (1–11)
Associated major hepatectomy, <i>n</i> (%)	0	35 (36.1%)	35 (20.2%)
Associated potentially contaminating procedure, <i>n</i> (%)	24 (31.6%)	14 (14.4%)	38 (22.0%)
Associated treatment of postoperative hernia repair, <i>n</i> (%)	11 (14.5%)	14 (14.4%)	25 (14.5%)
IRFA near biliary tract or vascular structure, <i>n</i> (%)	8 (10.5%)	4 (4.1%)	12 (6.9%)
Vascular clamping, <i>n</i> (%)	35 (46.1%)	39 (40.2%)	74 (42.8%)
Biliary cooling, <i>n</i> (%)	2 (2.6%)	1 (1.0%)	3 (1.7%)
Preventive cholecystectomy, <i>n</i> (%)	13 (17.1%)	18 (18.6%)	31 (17.9%)
Intraoperative transfusion, <i>n</i> (%)	5 (6.7%)	11 (11.3%)	16 (9.3%)

subcapsular hematoma were recorded, one of which occurred after IRFA treatment. Ten bilomas were noted, three of which occurred after IRFA. Only symptomatic bilomas were treated by percutaneous drainage. Four biliary stenoses were observed but only one was symptomatic and required a radiological procedure for stenting (Grade IIIa). These four patients had all received IRFA in liver segment IV.

Three intrahepatic vascular thromboses were observed; one patient (Grade IVa) required intensive care unit (ICU) treatment because of associated liver failure and hepatic abscesses. Three biliary fistulae developed in patients treated with IRFA plus resection. These were treated with percutaneous drainage and achieved spontaneous closure; one patient required subsequent intervention for drainage.

Six of the patients treated with IRFA combined with resection presented hepatic failure. One of these patients developed sinusoidal obstruction syndrome as a result of 12 cycles of preoperative chemotherapy with FOLFOX [folinic acid (leucovorin calcium), fluorouracil (5-FU), oxaliplatin] and required ICU treatment. Eighteen patients (nine treated with IRFA only and nine treated with IRFA combined with resection) underwent extrahepatic associated procedures and developed intra-abdominal extrahepatic complications including intraperitoneal abscesses, anastomotic leakage and occlusion. Patients treated with IRFA plus resection were more likely to be prone to blood loss, including acute postoperative bleeding and postoperative anaemia (11.3% of hepatectomies compared with 6.6% of lesions in IRFA-only patients), although the difference was not significant. Three

Table 3 Complications in patients treated with intraoperative radiofrequency ablation (IRFA) alone or with IRFA plus hepatic resection, by procedure according to the Clavien–Dindo grading system¹⁷

Procedures	IRFA only (n = 76) n (%)	IRFA plus resection (n = 97) n (%)
Procedures with complications	30 (39.5%)	45 (46.4%)
Complications of Grade II or lower	16 (21.1%)	23 (23.7%)
Complications of Grade III or higher	14 (18.4%)	22 (21.7%)
Immediate (<24 h)	0	4 (4.1%)
Early (1–30 days)	24 (31.6%)	33 (34.0%)
Delayed (>30 days)	8 (10.5%)	6 (6.2%)
Hepatobiliary complications	8 (10.5%)	18 (18.6%)
Intra-abdominal extrahepatic complications	9 (11.8%)	9 (9.3%)
Other complications		
Parietal	3 (3.9%)	5 (5.2%)
Pulmonary	6 (7.9%)	5 (5.2%)
Cardiac	2 (2.6%)	5 (5.2%)
Urinary	6 (7.9%)	4 (4.1%)
Neuro-psychiatric	2 (2.6%)	4 (4.1%)

patients treated with IRFA plus resection underwent emergency surgery for bleeding after hepatic resection. No bleeding was observed at any of the ablated sites.

Eight parietal complications were recorded in patients who had received previous abdominal surgery; these included four wound abscesses, one evisceration requiring surgery, one case of bleeding, one case of skin necrosis after incisional hernia repair, and one case of asymptomatic seroma. Three of the patients required incisional hernia repair during surgery.

Analyses of variables associated with complications of Grade III or higher are shown in Table 4.

Discussion

The parenchymal trauma of coagulative necrosis caused by IRFA differs from that induced by a hepatectomy. It is thus reasonable to expect different patterns of complications from the two approaches. The study of complications specific to IRFA is challenging as it is a technique often associated with resection. Although there are several publications on RFA-induced complications, many of these are mixed reports that do not distinguish between the strategies employed (open surgical, laparoscopic and percutaneous) or report on single approaches and are inconsistent in the complication factors identified, thus rendering analyses unreliable and controversial.^{19–21} The complications reported in the context of IRFA performed as a stand-alone procedure are based on small sample sizes, include only early (<30 days after surgery) complications, and rarely refer to sensitive complication

grading systems.²² Most research groups describe complication rates of 0–16% and mortality rates of 0–1.8%.²² The overall rate of complications after IRFA within the current study, as classified according to the Clavien–Dindo system, was 39.5%. The incidence of complications of Grade III or higher was 18.4%. In the prospective ARF2003 trial, which used the Clavien–Dindo system, the complication rates observed were similar at 44.8% for all complications and 12.2% for complications of Grade III or higher.³ When IRFA is combined with resection, reported complication rates rise to 12.1–31.0%, and mortality rises to 0–5.2%.²³ These rates should be compared with morbidity and mortality rates after hepatectomy alone, which are estimated at 20–50% and 0–5%, respectively.²³

The multivariate model revealed that surgery of >4 h in duration and the association of a potential contaminating procedure (e.g. an opening of the digestive tract such as in colectomy) were associated with greater risk for complications of Grade III or higher. Factors traditionally associated with surgical complications, such as American Society of Anesthesiologists (ASA) score,²⁴ previous surgery, body mass index and preoperative chemotherapy, were not associated with complications after IRFA. This suggests that IRFA has an additive rather than a specific effect on associated complications and using it in combination with a surgical intervention increases the risk for potential complications.

Indeed, IRFA also has an impact on liver function, albeit small. This factor should be noted by any surgeon dealing with complex bilateral diseases for which the consequences of exceeding the limits of liver function restoration may be critical. Theoretically, IRFA could induce liver failure in the treatment of large confluent lesions. Although IRFA is considered to be a parenchyma-sparing technique, it should be remembered that it is currently regarded as a complementary treatment to resection and not as a substitute. Some authors have advanced a step further and have reported multidisciplinary treatments involving an iterative use of IRFA in combination with hepatectomy and chemotherapy in the treatment of multiple metastases with good results.^{7,25}

Because of the tissular coagulation necrosis induced by IRFA, specific complications may differ from those induced by hepatectomy, especially with reference to haemorrhagic complications, which are a major drawback of liver resection and are rarely induced by IRFA. This is reflected in the results of the current study, in which haemorrhagic complications were reported twice as often in patients submitted to IRFA and hepatic resection at the same time. However, the fact that biliary ducts are very sensitive to heat represents the main limitation to using IRFA in the liver.²⁶ In the current series, biliary stenosis occurred in four patients with lesions in segment IV. It is now commonly accepted that lesions situated close to the main biliary duct are contraindicated for ablation.²⁰ The use of new ablative techniques, such as electroporation, in high-risk areas merits further investigation, although recent results have been disappointing.²⁷

Table 4 Univariate and multivariate analyses of predictive factors associated with morbidity in patients treated with intraoperative radiofrequency ablation (IRFA) only ($n = 76$) or IRFA plus resection ($n = 97$) across 173 IRFA procedures for liver metastases according to the Clavien–Dindo grading system

<i>n</i> (%)	Morbidity severity by Clavien–Dindo classification		Univariate analysis ^a	Multivariate analysis	
	Grade II or lower	Grade III or higher	<i>P</i> -value	<i>P</i> -value	OR (95% CI)
Procedure, <i>n</i> (%)					
IRFA only	62 (81.6%)	14 (18.4%)	0.49		
IRFA plus resection	75 (77.3%)	22 (22.7%)			
Age, years					
Mean ± SD	62.1 ± 13	57.7 ± 12.2	0.049 ^b	0.047	0.97 (0.94–1.0)
Median (range)	64.0 (21–98)	58.5 (31–78)			
Sex, <i>n</i> (%)					
Female	60 (88.2%)	8 (11.8%)	0.018	0.10 not retained	
Male	77 (73.3%)	28 (26.7%)			
ASA score, <i>n</i> (%)					
1	42 (82.4%)	9 (17.6%)	0.49		
2, 3	94 (77.7%)	27 (22.3%)			
Body mass index, <i>n</i> (%)					
≤25 kg/m ²	68 (81.0%)	16 (19.0%)	0.58		
>25 kg/m ²	69 (77.5%)	20 (22.5%)			
Previous abdominal surgery, <i>n</i> (%)					
No	25 (71.4%)	10 (28.6%)	0.21		
Yes	112 (81.2%)	26 (18.8%)			
Preoperative chemotherapy, <i>n</i> (%)					
No	42 (84.0%)	8 (16.0%)	0.32		
Yes	95 (77.2%)	28 (22.8%)			
Extrahepatic surgery, <i>n</i> (%)					
No	100 (87.7%)	14 (12.3%)	<0.001	0.32 not retained	
Yes	37 (62.7%)	22 (37.3%)			
IRFA impacts, <i>n</i> (%)					
1	49 (76.6%)	15 (23.4%)	0.14		
2	34 (72.3%)	13 (27.7%)			
≥3	54 (87.1%)	8 (12.9%)			
Pedicle clamping, <i>n</i> (%)					
No	79 (79.8%)	20 (20.2%)	0.82		
Yes	58 (78.4%)	16 (21.6%)			
Contaminating procedure, <i>n</i> (%)					
No	116 (85.9%)	19 (14.1%)	<0.001	0.004	3.72 (1.53–9.06)
Yes	21 (55.3%)	17 (44.7%)			
Operative time, <i>n</i> (%)					
≤4 h	100 (85.9%)	15 (14.1%)	<0.001	0.025	(1.12–6.30)
>4 h	32 (55.3%)	20 (44.7%)			

^aChi-squared test.

^bWilcoxon test.

OR, odds ratio; 95% CI, 95% confidence interval; SD, standard deviation; ASA, American Society of Anesthesiologists.

The most specific and practical concern with radiofrequency (RF)-induced necrosis is its ability to become secondarily infected. Complications such as liver abscesses resulting from proximity to a potential source of infection, such as an enterobiliary anastomosis, were reported 10 years ago by de Baère *et al.*²⁶ In the present study, it was observed that areas with necrosis induced by RFA have a propensity to become infected by occult bacteraemia. The opening of the digestive tract during a colectomy was enough to induce homing of bacteria in the RF lesion, an occurrence confirmed as an independent predictive factor of complications in the multivariate analysis. For example, the first stage of a two-stage liver procedure often includes a colectomy to treat the primary lesion and some IRFA of metastases in the left lobe before a right hepatectomy. An important issue to be addressed concerns whether changing the standard antibiotic prophylaxis to a therapeutic course is beneficial for the patient.

Overall, this study shows that IRFA is a safe technique and induces a low rate of specific complications. Nevertheless, the use of IRFA as an additive therapeutic tool is not without cost and thus it should not be considered as a simple, risk-free procedure that can be added to a complex procedure without consequence. The results of this series show that when IRFA is performed in association with long and complex procedures, it increases the rate of complications and especially the risk for liver necrotic abscesses in the context of a digestive tract procedure.

Acknowledgements

The authors thank the regional Ligue contre le Cancer (Gironde) for financing the radiofrequency generator and Jone Iriondo-Alberdi for proof-reading the manuscript.

Conflicts of interest

None declared.

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